

(3879) Shulman, Mulinos & Lieb (Coll. Physicians & Surgeons)

"These results show that a deep breath of air caused a constriction of the arterioles of the forearm; and that there is a greater and more lasting effect upon the vessels of the skin than upon those of the deeper structures." page 186, (3870)

(3975) Kesten, Mulinos & Pomerantz (Coll. Physicians & Surgeons)

"Dipropylene glycol, diethylene glycol, dioxane, carbinol, methyl carbinol and butyl carbinol when administered in adequate dosage orally or intravenously to animals cause extensive hydropic degeneration of the renal convoluted tubules, leading to uremia; less regularly, there is hydropic degeneration of the liver parenchyma. These compounds resemble each other in containing an ether linkage between glycol molecules. Ethylene glycol, ethylene glycol diacetate, and propylene glycol do not have such a structure, nor do they cause similar lesions in animals." page 465, (3975)

(3977) Mulinos & Shulman (Coll. Physicians & Surgeons)

"By means of 5 methods the vasomotor status of the hand has been studied in normal human subjects. These methods are described in detail. A deep inspiration causes marked vasoconstriction of the arterioles of the forearm and hand, but is especially marked in the skin of the fingers. The vasoconstriction from a deep breath is due to a reflex and is independent of the blood flow and blood pressure in the hand and of the temperature and moisture content of the inspired air. The constriction is exaggerated by any irritant or painful stimulus (pinch of skin, inhalation of smelling salts, tobacco smoke) which may accompany or shortly follow the deep breath." page 321, (3977)

(3983) Shulman & Mulinos (Coll. Physicians & Surgeons)

"The vasoconstriction from smoking may be due to a, irritation of the smoke; b, its nicotine content; c, mere inhalation. That nicotine is a minor factor is shown by the above experiments, and by observations of three smokers who smoked furiously and who showed nausea and vomiting but no vasoconstriction. It is concluded that the irritation and especially the deep breathing are responsible for the peripheral vasoconstriction from smoking." page 630, (3983)

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are responsible for the paroxysms of coughing that many cigarette smokers complain of. After putting them on diethylene glycol treated cigarettes they had less throat irritation and the paroxysms of coughing promptly disappeared. In practically every case, except in those cases where there was definite pathology, my patients were markedly improved.' Laboratory and clinical studies are in agreement that cigarettes containing diethylene glycol are less irritating than those containing glycerine." page 60, (3775)

(3669) Wallace, Reinhard & Osborne (NYU College of Medicine)

"The results of the work are shown in the accompanying table and charts. From these it is seen that the agreement with those of Mulinos and Osborne is remarkably close. The correctness of their statement that the smoke from cigarets which have been made with di-ethylene glycol as the hygroscopic agent is less irritating than those with no hygroscopic agent and much less irritating than those made with glycerin is thus confirmed. Further, it may be stated that the duration of irritant effects from the cigarets treated with glycerin is much longer than that from those treated with the di-ethylene glycol. With the experimental basis thus established, the clinical results obtained by Flinn are what would be anticipated and can be accepted as correct." page 309, (3669)

(3782) Lesser; Brooklyn, NY

"Sir: Your issue of March, 1936 carried an article by three members of Philip Morris & Co. entitled "Cigarette Industry Rules out Rule-of-Thumb." In the course of it the claim was made that 'use of diethylene glycol in place of glycerine constitutes one of the major advances in recent years in the manufacture of cigarettes.' The claim rested on two sets of tests, one made in the laboratory by Mulinos and Osborne, the other clinically by Frederick B. Flinn.

In justice to your readers, they should be informed that those tests have since been duplicated by other investigators who have published their reports, and that supplementary experiments have been made. These later findings throw serious doubts - to put it mildly - upon the validity of the 'major advance' claimed by the Philip Morris representatives.

The refutation of the claims for diethylene glycol as against glycerine as the hygroscopic agent in cigarettes has been published in the following reports:

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smoking of tobacco in the form of 'standard' cigarets produces in the great majority of normal individuals certain definite pharmacologic effects. ... Although not definitely proved, the evidence seems to indicate that nicotine is at least one of the toxic factors and that carbon monoxide and the products of the cigarette papers may be eliminated as offending mediums." pages 322-323, (3467)

(3558) Flinn (Dept. Physiology, Columbia University)

"An interesting case was reported by one of the doctors of a man who had gotten a 'piece of shrapnel in the lung during the war and found that he could not smoke more than 10 cigarettes of the regular brand a day. If he smoked more than this number he had a congestion of the lungs as if he had a severe cold, irritation of the respiratory tract which would require two months to clear up. When he was put on the diethylene cigarettes he increased the number smoked to 20 and 30 per day without noticing any effect on the lung tissue. An examination did not show any harsh breath sounds or any physical signs indicating an irritation or congestion in spite of the increased number he was smoking. He was changed to the glycerine cigarette without his knowing it and in a few days he had to cut down on the number he was smoking and complained of his lungs. On being put back on the diethylene cigarette the symptoms disappeared again.' We regret that the observations made by the group of 10 doctors were not in a shape to permit our tabulating them in a more scientific manner but the results remain the same. We have simply taken the clinical findings of the 10 men and analyzed them.

Summary: The combustion products of glycerine when it is used as a hygroscopic agent in cigarettes will under certain conditions cause an irritation of the throat. The combustion products of diethylene glycol cause only a slight irritation, if any, of the throat. There is some evidence that they may be beneficial where irritation is present." page 153-154, (3558)

(3775) Flinn (Dept. Physiology, Columbia University)

"The new studies reported to me by these doctors confirm my previous report. I have received similar reports from other doctors with a smaller number of observations; one of them said: 'This study of glycerine treated cigarettes shows that they produce considerable irritation to the throat and in many cases

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... Space in a letter does not allow a discussion of the conclusions reached by Haag, Ballenger, Johnson, Holck and Carlson, all authorities in their fields. Suffice it to say that they refute, specifically and in detail, the statements on the subject made in the article in your columns under the signatures of the tobacco company's employees. The Haag article meets the Mulinos-Osborne assertions; the others sharply contradict Flinn.

The company, for obvious commercial reasons, has continued its claim in a high-powered advertising campaign to the medical profession and the public, completely ignoring the published refutation of its contentions. Curiously enough, certain medical journals continue to publish full-page Philip Morris advertisements that make these same claims, despite the fact that the refutation is on records in the medical press itself.

But chemical engineers ought to know the facts behind the advertising. Those who read and may have accepted the Philip Morris contentions in your March, 1936 issue should, in the interest of professional objectivity, read the later developments as detailed in the reports I have listed." Letter to the Editor, Chemical & Metallurgical Engineering, page 443, (3782)

(3774) Fishbein (Editor, JAMA)

"Sir: In your August, 1937 issue, page 443, appears a letter signed by Milton A. Lesser, calling attention to some writings on the subject of cigarette smoke and its effects on the throat, which, it is claimed refute much that has previously been published concerning cigarettes made with diethylene glycol. The author of the letter sent to you is a chemist whose qualifications for judging clinical evidence are not apparent. The bibliography of Mr. Lesser, so far as it concerns glycerine, indicates that he has devoted himself largely to encouraging the use of that substance not only in cigarettes but in practically every other phase of human life. Certainly one would not be inclined to accept him as an unbiased critic in this field. Inasmuch as he has cited in his article the exceedingly brief bibliography which favors the use of glycerine glycol, it would have been much more fair to cite at the same time the bibliography of the articles prepared from a different point of view and based on far more extensive clinical evidence than is cited in Mr. Lesser's letter. The concluding paragraphs of his letter contain

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most of the tar and other products of incomplete combustion." page 1513, (3224)

(3773) Editorial (JAMA)

"Nine out of ten patients who had been given a proprietary elixir of sulfanilamide died recently in Tulsa., Okla., from anuria which apparently resulted directly from poisoning by this elixir. As we go to press, the record is swelled by the report of four additional deaths with another likely fatality in East St Louis. The product was prepared and sold by the S.E. Massengill Company of Bristol, Tenn. From tests by the chemical laboratory of the American Medical Association, this elixir appears to be a solution of approximately 40 grains of sulfanilamide to a fluidounce of a menstruum containing about 72 per cent of diethylene glycol (by volume) with flavoring. Apparently it is not known whether the toxicity of sulfanilamide is enhanced by the presence of diethylene glycol - or vice versa. The solvent, diethylene glycol, is itself not an indifferent substance. While its use is not permitted in food products because of the absence of any scientific evidence establishing beyond doubt its harmlessness when taken internally, it has long been utilized as a solvent in various industrial processes. The dosage of the elixir administered unquestionably contained a large amount of this substance. It would appear to be clear that the diethylene glycol or the diethylene glycol-sulfanilamide combination rather than the sulfanilamide was responsible; one of the patients had received tablets over a period of two weeks without any bad effects and then showed the typical train of symptoms after taking the elixir. From twenty-four to forty-eight hours after administration of the substance, nausea, vomiting, malaise and sometimes diarrhea developed; then complete anuria appeared within two to five days. The nonprotein nitrogen, urea nitrogen and creatinine rose rapidly. In the postmortem examination there was usually an accumulation of fluid in the serous cavities, with degeneration of the tubules of the kidney and a peripheral necrosis of the liver." page 1367, (3773)

(3778) Holck (University of Chicago)

"The results of these experiments place diethylene glycol between ethylene glycol and propylene glycol in toxicity. A high concentration of glycerin in the solid food (20 per cent) seemed harmless. Diethylene glycol in one fourth of this concentration in the fox-chow and in

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(3795) Ballenger & Johnson (Northwestern Univ. Med. Sch.)

"From a clinical study of the personnel forming the basis of this investigation, it is concluded that the hygroscopic agent used in cigarets is not a factor of importance in producing symptoms or in producing objective evidence of irritation of the nasal or throat mucosa or of the conjunctival sac. In fact, the control cigarets, in which no hygroscopic agent was used, seemed to produce somewhat more irritation both objectively and subjectively than those to which glycerin or diethylene glycol was added." page 80, (3795) Authors acknowledged grant from Glycerine and Soap Manufacturers Association

(3873) Geiling & Cannon (University of Chicago)

"The intelligent, energetic and cooperative manner in which the representatives of the American Medical Association, of the Food and Drug Administration, of the U.S. Department of Agriculture and of cooperating educational institutions worked brought this episode to a speedy solution. Had it not been for their splendid service the toll of human life would probably have amounted to several hundreds." page 926, (3873)

(3967) Ballenger (Northwestern University Medical School)

"Careful objective examination failed to show any significant difference in irritation of the mucosa of the nose or throat by cigarets moistened with glycerin, those moistened with diethylene glycol or those with no hygroscopic agent. The subjective symptoms or sensations of irritation, when present, were not marked enough in respect to distribution, character or degree to justify definite conclusions. Lymphoid hyperplasia of the pharynx does not appear to have any relation to the number of cigarets smoked." page 123, (3967)

(4332) Fabricant (Univ. Illinois College of Medicine)

"A method is described involving minute to minute readings of the pH values of the mucous membranes of the human throat for studying the irritating effects of cigarette smoke. The pH range of the clinically normal throat was found to vary from 4.9 to 8.0, the reaction in the majority of cases falling within the acid range. While the values varied with different persons, for the same subject the range was small and fairly constant. Cigarette smoke, regardless of the kind of cigarette, in

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by unknown changes in the film of mucus on the pharynx; however, if the measurements represent color, the average effect observed was that of blanching rather than reddening." page 225, (4712) Grant from Association of American Soap and Glycerine Producers, Inc.; also used in FTC Hearings, Docket No. 4794, its purpose unclear.

(4549) McNally, Bergman & Foster; Chicago, IL

"Experiments were performed on the irritating properties of smoke from tobacco treated with glycerine and diethylene glycol using the technique of Mulinos and Osborne. We could find no significant difference between the smokes from these two types of tobacco or between either of these and the smoke from plain tobacco." pages 251-252, (4549) Data have been used in court testimony, its purpose unclear.

Publications from District of Columbia, Missouri and Delaware. The diethylene glycol poisoning episodes led to articles written by personnel of the Food and Drug Administration. Laryngologists from Missouri contributed to the growing literature on irritant action of cigarette smoke:

(3976) Laug, Calvery, Morris & Woodward (FDA)

"The relative acute toxicities of some glycols and derivatives have been determined and the order of increasing toxicities is as follows: propylene glycol, diethylene glycol, ethylene glycol, diethylene glycol mono-ethyl-ether dioxin, and ethylene glycol mono-ethyl-ether. Three species were used: rats, mice and guinea pigs. A limited number of rabbits were used on diethylene glycol. The total number of animals used was over 2600. The rabbits, in comparison with other species, were found to have the lowest LD 50 for diethylene glycol. In fact, the lowest dose that killed some rabbits was the same as the estimated average dose that killed 105 persons." page 197, (3976)

(3986) Calvery & Klumpp (FDA)

"In September and October, 1937, approximately 203 gallons, of a total production of 240 gallons, or a proprietary remedy, 'elixir sulfanilamide,' was distributed. It was composed of 72 per cent diethylene

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openly asserts that there are no differences in the irritating properties of the various types of cigarettes now available to the American smoker. Further, there is no indication that cigarettes can be classified consistently as to the irritating quality of the smoke by supposedly normal human beings. In many instances, it has been demonstrated that the same kind of cigarette has at one time been called mild and at a subsequent period been pronounced irritating by the same person. In fact, a method for determining the irritating properties of cigarettes which relies solely upon the opinions of ordinary smokers cannot be called reliable. Patients, including physicians, will continue to smoke because they gain some pleasure from the habit, actual or imaginary. The only advice one can give conscientiously of that of moderation. There is no scientifically valid 'health' story when it comes to the subject of irritation." pages 312-313, (4622)

(4634) Holinger et al (Chicago)

"As a result of the measurements of blood vessels on 544 photographs of the uvula and soft palate of 136 subjects, the following observations were made: In a series of photographs of 12 subjects the measurement of the 105 measurable blood vessels showed that diethylene glycol treated cigarettes had a greater dilating effect on the blood vessels of the uvula and soft palate than either glycerine treated cigarettes or cigarettes containing no hygroscopic agent; however, the differences were so small that they were not statistically significant. ... The possible correlation between the effects of smoking on blood vessel diameter and the irritating properties of the smoke is discussed and it is concluded that the conflicting effects of some of the smoke constituents invalidate methods for evaluating smoke irritation which depend on measurement of blood vessel diameter or the attendant gross color changes." pages 778-779, (4634) Grant from Association of American Soap and Glycerine Producers, Inc.; also used in FTC Hearings, Docket No. 4794.

(4712) Andrews, Lenth, Staunton & Holinger; Chicago, IL

"The correlation between the reflectance readings and changes of color of the pharynx is discussed and it is concluded that the changes in reflectance probably are the result of changes in color, but that the evidence is insufficient to justify a more positive statement due to the possible complications introduced

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of 2.86, 3.18, and 2.68 for these same operations were found. These results indicate that the atmospheric dust is hygienically significant and within the size range of industrial dusts." page 51, (4896)

Harris enumerated in his SOA report the following health effects of nicotine unrelated to suspected carcinogenic action: coronary heart disease (3459) (4035) (4122) (4652); peripheral vascular disease (3470) (3654) (3880); disturbances in reproduction (4357), pregnancy (2960) (3567) (4033) (4165), breast feeding (4252); and difficulty in stopping cigarette habit (3661) (4150). These articles are recalled here to emphasize that prior to 1950, there was no published suspicion that nicotine caused cancer.

Physicians Against Cigarette Smoking

There were three lay publications that discussed the background of physicians and scientists who joined the anti-smoking movement: Kenyon, from Axton-Fisher Tobacco Company, Louisville KY (3405); Porter, from a Southwestern College of Mines and Metallurgy (4755); and Gottsegen, an economist from Columbia University (4004). The latter author discussed in *Tobacco*, not only its consumption in the United States, but alleged health effects of tobacco, including cancer of lips, tongue, mouth, throat, lungs and esophagus. The title of the book probably misled Larsen, Haag & Silvette and was omitted in their *Tobacco Monograph* (6101). The pertinent quotations from Gottsegen is included in the list below as examples of prevalent

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terms of cigarette-smoke-effect remains to be seen."
page 194, (3978)

(3979) Proetz; Washington Univ. Sch. Med., St. Louis, MO

"We had to devise some means also for getting hold of the tar so that we could apply it in some sort of standard way to a human throat. It is going to have to be done in a large series of cases. We have already made something short of 1,300 observations only to conclude that routine human observation of the throat is not very reliable. We have devised a colorimeter which will measure accurately the color changes in the throat because we do not know for what we are looking. We do not know that the initial change may not be a paling instead of a reddening. There may be an astringent effect first or last. At any rate there are certain effects that we have noted that we can put to use. For instance, we will make use of what is known as the impingement effect to collect the tar from the cigarette. I will show you how it works. If we blow the smoke from a cigarette through a glass tube, against a sheet of paper, practically none of it sticks, as I told you before in regard to the little white paper box. However, if we blow it with some force through a capillary tip, so that eddies are formed, the tar is forced against the paper more or less forcibly and sticks there and can be gathered. That is the principle, of course, utilized in the cigarette holders employing a cigarette as a filter. It is simply a series of capillary tubes. However, we have rigged up a contraption of glass tubes, so that the smoke which we are studying can be deposited right on the tip of a glass rod. We can pile up the tar and gather the fumes in balloons and apply them to the throats of human subjects. As I said before, there are many variable factors that control the color changes in the throat, the temperature of the room, the condition of the climate, the patient's condition of health, the patient's recent eating of a meal, the patient's having a cold, and what not, so that literally thousands of these tests will have to be made before we can arrive at anything of scientific value. If these very few short descriptions of a laborious job are of any value at all, it is probably to point out that the problem is an involved one and that one must investigate the source of any statements made about tobacco smoking before giving them any credence." pages 245-246, (3979)

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an insinuation which cannot be supported by any evidence." page 501, (3774)

The four articles cited by Lesser were later acknowledged by the tobacco company. Haag's research support from the tobacco company was not cancelled because of scientific disagreement with Mulinos, Osborne & Flinn.

Publications from Illinois. The poisoning episode with sulfanilamide suspended in diethylene glycol coincidentally occurred while the glycol was being introduced as a hygroscopic agent for tobacco. In spite of animal studies denying that inhalation of diethylene glycol was unlikely to cause toxicity, the further use of the hygroscopic agent was stopped. I do not have any publication on the year it occurred. Most writers who were critical of any form of human use of diethylene glycol were from Illinois. McNally, from Rush Medical School, published the suspected effects of cigarette smoke tar in the 1930's and then joined the anti-diethylene group marked by another article in the 1940's (see also Chapter III, page 214).

(3224) McNally (Rush Medical College):

"The tar of cigarette smoke contains nicotine, phenolic bodies, pyridine bases, and ammonia, irritants which could account for 'cigarette cough,' the chronic bronchitis of the cigarette smokers, the leukoplakia in heavy smokers, and the recorded increase of cancer of the lung. The temperature is not an important factor unless the cigarette is burned down to the last centimeter, when the hot smoke becomes more irritating. With a tarry residue of 4.84 to 15.29 per cent, a definite risk attaches to the smoking of a cigarette, especially since 6.56 to 11.58 per cent may be absorbed or retained in the body. Cigarettes should not be smoked too short, as the last two centimeters retain

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D. OCCUPATIONAL/ENVIRONMENTAL FACTORS

Prior to 1950, there was considerable literature supporting the causative role of occupational exposure and environmental factors in lung cancer patients. During the 1940's, there were more medical researchers who studied non-smoking causes of lung cancer, than those who published articles blaming cigarette smoking as the cause. The situation can be summarized as follows: First, the appearance of monographs, review articles and original studies on occupational and environmental carcinogens far exceeded those suggesting cigarette smoking or other personal habits as cause of cancer; Second, majority of clinical articles on lung cancer that mentioned cigarette smoke as an associated factor also discussed the coincidental association with occupational and environmental factors; Third, some constituents of coal tar that were chemically isolated, synthesized and tested for animal skin carcinogenicity, were also detected in cigarette smoke leading to a conflicting interpretation of relevance of animal skin painting to human lung cancer; Fourth, some industrial chemicals that were suspected human carcinogens were also detected in cigarette smoke and this contributed to further suspicion that cigarette smoking caused lung cancer without considerations of relative concentrations between work environment and cigarette smoke; and Fifth, the animal and human observations incriminating fossil fuel products and vehicular combustion emission as pulmonary

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(4063) Mulinos & Shulman (Coll. Physicians & Surgeons)

"Using 5 different methods, an analysis of the response of the peripheral vascular system to smoking and deep breathing has led to the following conclusions: Deep breathing alone can account for the greater part of the decreased blood inflow rate, the loss of hand volume and the drop in skin temperature of the hand resulting from the inhalation of cigarette smoke. The subjects who did not inhale cigarette smoke showed a greater vascular response on the hand from 10 deep breaths than from the puffing, and a lesser response than those who inhaled the cigarette smoke. Inhaling the smoke from denicotinized cigarettes resulted in as great and occasionally greater vasoconstriction than the inhaling of the smoke from a standard brand cigarette. The degree of response of the peripheral vascular system varies markedly among individuals and in the same subject from day to day. The vasoconstriction due to smoking lasts about 15 minutes (7 to 45). These figures are at variance with the conclusion that 'If ... a patient should smoke 1 cigarette an hour he would depress his peripheral circulation during the entire day.'" page 719, (4063)

(4369) Mulinos, Pomerantz & Lojkin (Coll. Physicians & Surgeons)

Metabolism and toxicology of ethylene glycol and ethylene glycol distillate. Reprint not available.

(3467) Wright & Moffet (NY Postgraduate Med Sch & Hosp)

"Nicotine has long been considered the most important factor in the causation of effects from cigarets. The vital consideration is not how much of this poison is in the tobacco but how much is actually absorbed through the mucous membranes and alveolar walls into the blood stream. The tobacco itself varies widely in nicotine content. For example, the average nicotine content of various tobacco is as follows: Havana tobacco, 1.5 per cent; Maryland tobacco, 2 per cent; Virginia tobacco, 6 per cent; Kentucky tobacco, 8 per cent. The amount of nicotine and other products in the inhaled smoke is influenced greatly by, first and most important, the amount of moisture present, and also the tightness of packing, the length of the cigarette and the rate of smoking. The drier the tobacco, the greater the destruction of nicotine. Dixon states that the water content of the tobacco is more harmful to the smoker than the original nicotine content. ... The

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much smaller concentrations in the drinking water was distinctly harmful as judged by cases of mortality, stunted growth in the young, and impaired reproductive capacity. ... In an eleven weeks experiment, younger adult female rats gained about the same in body weight as control animals when a high concentration of glycerin (20 per cent) was mixed with their solid food. Similar concentrations of commercial diethylene glycol killed all rats within about two weeks, and even 10 and 5 per cent proved fatal to some of the rats. Diethylene glycol is even more toxic when added to the drinking water. When the rats drank from a 5 per cent solution, the average duration of life was only eight days." page 1519, (3778)

(3779) Holck & Carlson (University of Chicago)

"Our data give no indication that cigarettes can be classified consistently as to the irritating quality of the smoke by supposedly normal humans, although Flinn's report suggests patients with various affliction due to smoking are able to judge differences in cigarettes similar in nature to ours. In many cases the same kind of cigarette was at one time called mild and at a subsequent period pronounced irritating by the same person. We believe, therefore, that a method for determining the irritating properties of cigarettes which relies solely upon the opinions of ordinary smokers cannot be considered reliable. The smoke of these 3 types of cigarettes increases the acidity of water to an equal extent, as determined by exact pH tests." page 307, (3779)

(3792) Schoeffel et al (AMA Chemical Laboratory)

"Elixir of Sulfanilamide-Massengill in the specimens examined was found to consist essentially of sulfanilamide 10 Gm. in 100 cc. of a solution of approximately 72 per cent diethylene glycol and water 25 per cent by volume, to which had been added flavoring and coloring material. Diethylene glycol in the doses given was the causative agent in deaths. Pathologic results reported herewith both on animal and on man, as well as many reports received by telephone and telegram, indicate that, in cases of death following the administration of Elixir of Sulfanilamide-Massengill, anuria was present." page 1539, (3792)

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number of patients found suffering from cancer of the respiratory tract. Though literature reveals that for certain individuals smoking is injurious, much more work must yet be done to prove that the abnormal actions of organs, produced by nicotine and other chemicals found in smoke, are lasting. Medical and other researchers who are seeking the truth on this subject are increasingly calling attention to the damaging effect on the human body produced by smoking, and especially by inhaling smoke. Because of the carcinogenic action of tar found in tobacco smoke there is need for the closest observation of the air passages, and most skillful diagnostic acumen when patients habitually smoking and inhaling, present themselves for medical care." page 349, (4064)

(4133) Crampton; U. S. Army, New York, NY

"The use of cigarettes has increased eleven times since the beginning of the world war. It is still increasing. Soldiers smoke more than civilians. This will probably lead to an even larger per capita consumption of cigarettes in the near future. The toxicity potential of smoking is a matter important to the physician, both military and civilian. The physician must recognize smoking as a general human phenomenon. He must be understanding and deal with the problem accordingly. The physician who expects co-operation when modifying his patients' smoking, must consider the 'pleasure factor.' It is important not to lose sight of the fact that people smoke for enjoyment. It is also evident that smokers cannot be diverted to any great extent to cigarettes which are lacking in this respect, either because of special processing, for hygienic purposes, or due to a deficiency in inherent quality. General prohibitions are not indicated. A final complete answer is yet to be formulated, and it should be reasonable, scientific, and above all, human-wise." page 11, (4133)

(4240) Johnston; Wallasey, GBR

"Nicotine was given hypodermically, in doses ranging from gr. 1/50 to gr. 1/10, to 35 volunteers, some being smokers and others non-smokers. Symptoms induced by the injections were described as 'swimminess' or 'muzziness'; large doses caused toxic symptoms in addition, including rapid and forcible cardiac action, vomiting and syncope. Smokers could tolerate considerably larger doses than non-smokers. Intravenous

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The last pertinent article on ethylene glycol was by Wiley, Hueper, Bergen & Blood from the Haskell Laboratory of Industrial Toxicology, DuPont, Delaware. They reported the formation of oxalic acid following oral administration in dogs (3853). Hueper continued his interest in toxicity of urinary system by describing chronic bacterial cystitis in the dog (4147) and pursuing further mechanism of urinary bladder carcinogenesis (see above, page 423).

Constituents of Tobacco Smoke

Prior to the 1940's, the most comprehensive review on the biochemistry of tobacco was by H. Bruckner, from Berlin (3657). This article, as well as 3 other German articles on nicotine (3565) (4346) (4464) need English translation because it would be important to evaluate the opinion of Bruckner and other German chemists on suspected carcinogenic action of tobacco smoke. There were publications on constituents of cigarette smoke such as acid bases, ammonia oxides and alkaloids (3569) (3655) (3768) (3769) (3971) (4894) (4932). A comprehensive review on constituents of cigarette smoke was not available in English during the 1940's.

Nicotine content. Jensen and Haley, from the Pennsylvania Agricultural Experiment Station, was one of the early American tobacco chemists who measured the nicotine content of cigarette smoke generated by a machine (3561). They concluded that

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(4456) Maris (affiliation unknown)

"Pictures showing wounded soldiers lying on cots or stretchers smoking cigarets dramatize the important fact that nothing is left undone to improve the morale of our fighting men. Yet these same pictures may do a dis-service to Army doctors, for if the wound involves the circulation, particularly of the arms or legs - and most war wounds do - the chances are the soldier wouldn't be smoking." page 740, (4456)

(4461) Morton; Middlesex, GBR

"The incidence of bronchitis, atelectasis and broncho-pneumonia after abdominal operations and 'gas-oxygen-ether' has been studied in 1257 cases in adults. The use of omnopon-scopolamine, a mild respiratory depressant, for premedication was associated with a slight but not significant increase in pulmonary complications, as compared with the use of atropine alone, which has no depressant effect. The combined figures for all types of abdominal operations show that the morbidity-rate for smokers taking more than 10 cigarettes or 1/2 oz. tobacco a day is about 6 times that for non-smokers. Smokers are more likely to develop complications associated with serious constitutional disturbance." page 370, (4461)

(4827) Editorial; JAMA, Chicago, IL

"For some years *The Journal of the American Medical Association*, the state medical journals and most other medical publications have carried the advertisements of the various companies that manufacture cigarettes. Actual surveys indicate that the majority of physicians themselves smoke cigarettes. Extensive scientific studies have proved that smoking in moderation by those for whom tobacco is not specifically contraindicated does not appreciably shorten life. Postmortem examinations do not reveal lesions in any number of cases that could be definitely traced to the smoking of cigarettes. From a psychologic point of view, in all probability more can be said in behalf of smoking as a form of escape from tension than against it. Several scientific works have been published that have assembled the evidence for and against smoking, and there does not seem to be any preponderance of evidence that would indicate the abolition of the use of tobacco as a substance contrary to the public health. Physicians are no doubt familiar with the articles that have been

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glycol, 8 per cent sulfanilamide, and 20 per cent of essentially flavors, saccharin, caramel and water. Each fluid ounce contained, therefore, approximately 21.5 cc. of diethylene glycol and 2.7 grams of sulfanilamide. The data on 105 deaths associated with the consumption of this drug are available for toxicologic study. In addition, reports concerning 248 individuals who consumed varying known amounts of the drug but survived are also available for study. The information which serves as the basis for this report was obtained principally from physicians, patients and relatives, and by the inspectors and scientific personnel of the Federal Food and Drug Administration. In addition, collateral and supportive data were obtained through the generous cooperation of pathologists, pharmacologists, and the American Medical Association, by whom various aspects of the mass poisoning were likewise studied. A number of reports relating to the tragedy have already been published. A study of the literature on human toxicology reveals few reports of mass poisoning of similar magnitude.

Consideration of clinical experience with sulfanilamide, pharmacologic and toxicologic studies of both diethylene glycol and sulfanilamide, and study of the pathology of fatal cases of 'elixir sulfanilamide' poisoning leads to the inescapable conclusion that the poisonous ingredient in the 'elixir sulfanilamide' was diethylene glycol. It is unlikely that the sulfanilamide contained in the preparation had a determinative deleterious effect in the majority of the cases. On the other hand, it is not unreasonable to suppose that the presence of sulfanilamide placed an added burden upon organs already damaged by the diethylene glycol." page 1105-1106, 1008, (3986)

(4247) Morris, Nelson & Calvery (FDA)

"The results of this investigation illustrate clearly the advantage of the long-time chronic toxicity study. The results obtained by continuing the experiment for two years that would not have been noted if it had been discontinued at the end of one year were the occurrence of urinary calculi in each of the series of the animals receiving ethylene glycol and diethylene glycol. It is possible also that the microscopic lesions and testicular enlargement observed would not have been as distinctly different between the experimental and control animals if the experiment had been continued for only one year. As we have emphasized elsewhere chronic toxicity studies should be continued

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as occupational activities, diets, medicines and medicinal devices, cosmetics, wearing apparel, building materials, habits and customs, climate, fauna, contaminants in drinking water, atmospheric air, foodstuffs, and - in recent years - procedures of warfare." pages 4-5, (4804)

The third monograph by Hueper was entitled *A methodology for Environmental and Occupational Cancer Surveys* which carried Hueper's affiliation as Chief, Cancerigenic Studies Section, National Cancer Institute (4210). Hueper also contributed to periodicals on the subject of industrial cancer and its control (4340) (4637) (4638) (4943) (4944). There was no mention of cigarette smoking in any of Hueper's monographs and periodical reviews appearing during the 1940's.

Willis, in his monograph entitled *Pathology of Tumors* (high-light publication) wrote a brief survey on occupation and cancer:

"The association of particular kinds of tumours with certain occupations is sometimes too obvious to require statistical analysis, e.g. chimney-sweep's cancer, cotton-spinner's cancer, 'aniline' cancer of the bladder, carcinoma of the lung in the miners of Schneeberg and Joachimsthal, and osteosarcomas in the dial-painters of New Jersey. However, apart from immediately obvious occupational associations of this kind, statistical analysis shows significant occupational differences in the incidence of particular tumours or of 'cancer' generally. Thus the Registrar-General's report on cancer deaths in England and Wales for 1930-1932, showed general rates much higher than the average for furriers, glass-blowers, tin and copper miners, stevedores, curers, leather-dressers, etc., and rates much lower than the average for teachers, clergymen, retailers, telephonists, etc. Or, as an example of occupational differences of a particular kind of tumours, the mortality rates from cancer of the buccal cavity and pharynx were much higher than the average in barmen, furnacemen, dock labourers, horse drivers, general labourers, hotel keepers, etc., and much lower than the average in retailers, clergymen, tram drivers,

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More than a statement on occupational cancer, Hueper's *Occupational Tumor* stands today as a singular contribution to the modern theory of environmental carcinogenesis. But, when it was published in 1942, the book failed to attract attention commensurate with its significance. The timing of its publication could hardly have been worse, coming as it did only weeks after the Japanese attack on Pearl Harbor. In Hueper's words, 'It was a difficult time to try to interest people in the loss of life.'

Among the multiple carcinogens which Hueper identified in *Occupational Tumors* were benzidine, beta-naphthylamine, and several other aromatic amines used in a wide variety of industrial processes and associated with a major increase in bladder cancer, most notably among exposed dyestuffs workers. In 1974, 32 years after the publication of Hueper's text, the newly established federal Occupational Safety and Health Administration (OSHA) was prompted to adopt national standards intended to limit worker exposure to 14 carcinogens. Among the 14 were benzidine, beta-naphthylamine, and other aromatic amines - the very same substances which Hueper had documented more than three decades before as potent occupational carcinogens. What were the institutional forces responsible for this tragic hiatus? Hueper's career provides some instructive insights into the barriers to effective preventive policies." pages 133-135, (7701)

Hueper's monograph described above is a highlight publication (4207); the book was followed by a Public Health Report on *Environmental and Occupational Cancer*. Hueper defined environmental carcinogens as follows:

"Any physical, chemical, or parasitic agent forming a part of our natural or artificial environment that, on proper exposure, directly or indirectly elicits cancerous growths in one, several or all types of human tissues, represents an environmental carcinogen. Although some of these agents, like solar rays, soot, and arsenic, have a practically universal distribution, the occurrence of demonstrable environmental cancers is restricted, as a rule, to regions or to groups of individuals having a particularly intense, prolonged, or otherwise positive contact with these carcinogenic agents. Exposure to these factors is related to a great number of highly diverse environmental conditions, such

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opinion prior to 1950. Physicians who were discouraging tobacco smoking for medical reasons based their opinion on reportedly high incidence of coronary heart disease among cigarette smokers. Cancer was rarely mentioned other than that tobacco smoke was one of several "irritants" suspected of causing cancer.

(2301) Kellogg; Superintendent, Battle Creek Sanitorium and
Editor of Good Health:

"Besides the nicotine there are all the other poisonous products which are always present in smoke, creosote, pyridine, prussic acid, furfural. The complacency with which smokers and sometimes non-smokers, ladies, perhaps, often sit for hours in a room the air of which is blue with tobacco smoke, is an evidence of the blunting effect of nicotine upon the normal sensibilities. Smoke from any other source would not be tolerated. Yet smoke is smoke, and tobacco smoke does not differ essentially from other smoke except by the addition of nicotine, and other poisons much worse than those of ordinary smoke. The well-known irritating effects of smoke upon the respiratory membranes easily explain the injurious effects from tobacco smoke observed in the throats of smokers. Smoker's sore throat is a condition very familiar to throat specialists. The highly irritating and injurious effects of tobacco smoke in cases of chronic disease of the throat and lungs from other causes is also well known. So long as the patient continues to smoke his throat maladies are incurable; but from the moment he lays aside his pipe or cigar, recovery begins." pages 49-50, (2301)

(2632) Rolleston; University of Cambridge

"The medical aspects of tobacco interest us all in our capacity as medical advisers of others, and, in addition, probably a certain proportion from a personal point of view. As in the case of alcohol, our opinions are inevitably colored by our own tastes, for the teachings of the laboratory cannot always be rigidly applied to human practice or correspond with the empirical lessons of a lifetime. Animal experiments cannot well take into account idiosyncrasies, and with regard to alcohol and tobacco personal peculiarities are so important that they must often over-rule any hard-and-

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over long periods of time especially in the case of those substances that are to be included in the diet of man or are to be administered as therapeutic agents or applied as cosmetics repeatedly over long periods of time." pages 271-272, (4247)

(4624) Fitzhugh & Nelson (FDA)

"Bladder tumors occurred in about half of the rats on the 4 per cent and 2 per cent concentrations, and in none of those on the 1 per cent concentration of diethylene glycol. The tumors of the bladder were both papillary and intramural. The former were generally benign, while some of the intramurally located tumors showed varying degrees of malignancy. On the 4 per cent level of diethylene glycol in the diet, lesions in the kidneys of rats were moderate to marked in degree, on 2 per cent they were slight or absent. Eight of the 12 rats had kidneys which were hydronephrotic, enlarged, fibrous, granular or combinations of these. Microscopically, the chief lesions were varying degrees of focal tubular atrophy and hyaline case formations." page 43, (4624)

(3978) Proetz; Washington Univ. Sch. Med., St. Louis, MO

"Regarding the reliability of simple clinical observation as a basis for statistical studies of the pharynx, even under the best conditions and with the problem clearly defined in the mind of the examiner, we find a diversity of opinion reaching 70 per cent. Regarding the comparison of subjective irritation with objective changes, as seen in the clinic, we find a discrepancy in 54 per cent of the cases, when these are divided into four broad categories. Even when they are divided into two classes, 'obviously inflamed' and 'obviously not inflamed,' the discrepancy still reaches approximately 7 per cent. Just what are the objective changes produced in the mucosa by the protracted action of cigarette smoke has not been determined. It is not at all certain that they may be classified in terms of color, or even that progressive irritation results in progressively heightened color. It would of course be desirable, in the light of the minute changes which are likely to occur, to eliminate the human element as much as possible in recording them. Whether a colorimeter can be devised which will provide a graphic record of small, variously colored areas of the mucosa and whether after that, one can learn to interpret such a record in

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published on the effects of tobacco on the circulation, the blood, the gastric acidity and other physiologic mechanisms within the human body. This editorial will not attempt to summarize the evidence or to derive any positive conclusions from it. It is concerned, rather, with the manner in which leading manufacturers have begun to lean so heavily on reference to the medical profession in promoting their products.

The advertising accepted by *The Journal of the American Medical Association* has always been screened through various committees, and the evidence in behalf of the statements made has seemed to be sufficient to warrant the statements that appear in the advertisements. Gradually, however, claims point more and more toward the single factor of the extent to which certain cigarettes irritate the throat. One product is said to be less irritating than others, and the suggestion is made that persons who suffer irritation from other cigarettes try the one that is said to be less irritating. Another is said to be always milder; a third is said to be absolutely free from throat irritation as based on tests conducted under the supervision of physicians." page 652, (4827)

Most of the above are derived from Harris' selected references. However, I have selected sentences that do not necessarily support Harris' summary statements. Instead, the quotations imply that tobacco smoke is a general "irritant" which was the subject of research projects supported by tobacco companies. Since "irritants" are suspected to be a cause of lung cancer prior to 1950, the tobacco companies cannot be criticized for misdirected research funds.

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nicotine content varied inversely as the moisture content of cigarettes. They also reported that nicotine content in side stream smoke varied with moisture content. The nicotine content was also influenced by portion of tobacco used for manufacture of cigarette (3560), and manner of curing tobacco leaf (3659) (3660) (3794).

Health effects of nicotine. From the time leaf tobacco was sold on the auction floor until it was finally made into a cigarette, a number of manufacturing operations occurred, including steaming and redrying of the leaf (4896). McCormick, Smith and Marsch from North Carolina State Board of Health studied the health hazards in tobacco industry:

"The results of the study indicate that certain health hazards may exist in industrial establishments engaged in processing leaf tobacco. Of these, those due to the inhalation of free silica and insecticide dust are probably of most importance. This statement is made with the realization that at the present time insufficient evidence exists relative to the hazard associated with the inhalation of nicotine. Only the nudging-blending, stemming, and cleaning operations were found to present health hazards. A tentative maximum allowable concentration of total dust of 10 MPPCF is suggested. The maintenance of atmospheric dustiness below this value should control satisfactorily all of the other associated health hazards. The free silica content of dusts found in these processing plants ranged from approximately 22 per cent to 58 per cent by weight, with no significant difference between the various operations studied. A significantly lower free silica content of atmospheric dust than settled dust was observed. The Goldman modification of the hydrofluosilicic acid method of free silica analysis compared favorably in accuracy with the X-ray diffraction method. The geometric mean particle sizes of the atmospheric dust showed average values of 0.90, 0.79, and 0.85 microns respectively for the hanging-blending, stemming, and cleaning operations. Respective standard deviations

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recently investigators have turned their attention to the possible influence of the increased use of smoking tobacco (especially the marked increase in the use of cigarets)." page 2218, (4156)

(4209) Hadfeld & Garrod; St. Bartholomew's Hospital, London, GBR

"With the increasing tendency to regard cancer as the product of long-continued irritation, it is inevitable that attention should be directed to inhaled irritants. Gassing during the war and its sequelae apparently do not predispose to cancer, nor is there any good reason for incriminating tobacco smoke. There is no statistical evidence to indicate that exhaust gases from petrol engines are carcinogenic, but a study of occupational distribution extensive and detailed enough to yield significant data bearing on this point has yet to be made. Brockbank, who attempted such a study, found that the occupational labels found in ordinary clinical records were altogether inadequate for deciding whether there had been any unusual exposure to dust or fumes; a detailed personal interrogation could alone decide this. Since the exhaust of an internal combustion engine contains both lubricating oil and soot, substances both of which are carcinogenic in certain forms, the effect of modern traffic on city atmospheres is naturally regarded with suspicion, although Campbell reports negative results from exposing mice to an atmosphere polluted with the exhaust of a petrol engine. He has, however, observed an increased frequency in lung tumours among mice exposed to an atmosphere containing dust from tarred roads, and this effect was not altogether prevented by previous extraction of the tar in the dust with benzene." page 223, (4209)

(4233) Harrison; Shreveport, LA

"The inhalation of dust, motor fumes and tar fumes have been given considerable consideration. Automobile fumes and tar fumes have both been considered very seriously because the increase in the incidence of bronchogenic carcinoma has run almost parallel with the development of the automobile and the consequent use of tar in the roads. To date there has been no satisfactory evidence presented to support the case of street dust as the cause of lung cancer. Tar does have a little more support. Moller painted the backs of young rats with tar and obtained the cornified squamous epithelial variety of lung carcinoma in all animals that survived the 300 days of painting. However, another investigator

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none of it is used and cancer of the lung is a rarity. This comparison, however, does not hold in every country and the case against tar is, therefore, not settled. Closely linked with the possible role of tar is the evidence against tobacco. The recent sale of a cigarette holder which encloses a cigarette through which the smoke is filtered is a graphic demonstration of the amount of tar resin introduced into the bronchial passages in the course of a day. The incidence of smokers in some series is remarkably high although Vinson noted the fact that only seventy of 140 cases of carcinoma of the tracheo-bronchial tree, at the Mayo Clinic, were smokers. Tobacco smoke as a lung irritant may be considered at least a possible cause of pulmonary malignancy in susceptible individuals but not necessarily a major factor. In any event, all known etiologic agents have in common the one characteristic of producing pulmonary irritation and, since they are so diverse, the only conclusion possible is that such irritation is the real activating or causative factor in the disease. Simonds asserts that the reduction of all the present known facts to one formula is a positive result of the work so far performed." page 363, (4049)

(4095) Tripoli & Holland; Charity Hospital, New Orleans, LA

"The etiology of carcinoma of the lung is still not clear. The factors most frequently emphasized include dust, chemicals, gases, fumes and tobacco, as well as such pre-existing diseases as influenza, tuberculosis, and syphilis." page 560, (4095)

(4096) Coleman; Columbia, SC

"The increased incidence of cancer of the lung is both relative and real. The wider use of coal tar products exhaust gases from automobiles, tobacco smoking, and other agents resulting in chronic pulmonary irritation are considered to account for the real increase in cancer of the lung." page 46, (4096)

(4156) Menne & Anderson; University of Oregon, Portland, OR

"Contamination of the air in areas of congested traffic and industry is receiving increased attention. Rosedale and McKay, and Dressler and Weigl incriminated chromate dust as provocative in chemical industrial workers. Continued emphasis is being placed on the role of coal dust, chemical agents, radioactive substances and silicosis in mining and other industries. More

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silica dust, or where inhalation of tar fumes is likely. In the well-known mining district of Schneeberg many cases of carcinoma have developed in the workers. There many investigators attribute the carcinoma to the inhalation of arsenic and cobalt, while others feel that it may be due to the inhalation of silica dust." page 913, (4087)

(4784) Simonds & Anderson; Omaha, NE

"To explain the etiology of lung cancer many theories have been suggested, particularly in connection with the observation that the incidence is increasing. The relationship of chronic inflammatory changes following influenza or the inhalation of certain dusts and gases has been suggested. None of these factors have been proved to have definite etiology in lung cancer. The only carcinoma of the lung which can be correlated clinically with a known cause is the Schneeberg lung cancer developing in miners in certain regions of Saxony. A combination of arsenic and radium emanation in the dust of the mines and the local mechanical irritation of inhaled sharp dust particles seem to be etiological factors in this type of lung cancer." page 311, (4784)

(4962) Ryan & Myer, U.S. Naval Hospital (? location)

"The etiology of bronchogenic carcinoma has been the subject of much study and, except for a few instances where working conditions have been shown to have a very definite influence as a causative factor, no definite cause is known." page 863, (4962)

Group (b) Articles on health hazards of occupational/ environmental factors with tobacco smoking mentioned but no opinion on preferential cause.

(4049) Higgins; Medical College of Virginia, Richmond, VA

"To what extent tar particles contribute to the increase in pulmonary cancer is highly debatable. It is known that tar both clinically and experimentally is a potentially carcinogenic substance and in some countries its use on the roads has been followed by an increase in pulmonary neoplasm. Goltz has contrasted the annual application of half a million tons of tar on the roads of the United States with the fact that in Hong Kong

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large proportion of cigarette smokers who practice inhaling." page 185-186, (3047)

(3569) Sharlit; New York

"The medical profession, if it is to concern itself in the matter at all, should take the following position regarding cigarettes: Tobacco smoke cannot be considered harmless. The manufacturers of tobacco products are to be encouraged in their efforts to modify the art in behalf of a more harmless smoke, but, however good the achievement, the introduction of a filtering material into the smoke stream will effect a still safer smoke. The profession should assist in the production of a consumers' psychology sympathetic to the introduction of filters into cigarettes. The physicians of the United States never have endorsed a tobacco product and probably never will, but they should be prepared to endorse and encourage the use of principles in the practice of the art where it is evident that such practices lead to the production of a less harmful smoke." page 116, (3569)

(3663) Ingalls; Associate Editor, Scientific American

"What, then, of smoking? Has science an answer to the question whether smoking is harmful? How much ought an individual to smoke?

Science need not answer these questions for they have already been answered by tests on more than 100,000,000 guinea pigs - those of us who smoke. Most smokers - probably all smokers - are doubtless harmed to some extent, usually not great, by smoking. Likewise, most or nearly all smokers derive some pleasure and satisfaction from smoking. As Professor Mendenhall says, a packet of cigarettes is a 'packet of rest,' and the same is true of cigars and the pipe. That is, tobacco is a mild sedative - it quiets our nerves. Most of us contrive, generally without thinking, to adjust the extent of our smoking in such a way as to make a net gain of smoking satisfaction over smoking harm. The few who do not, do not employ their entire intelligence or else they are too weak to do so even when they sense its need. As it probably will do little or no good to preach to this minor fraction, we pass on. The average intelligent smoker senses when he is smoking too much, because he does not feel well, and he eases off, often unconsciously. Scientific experiments, then, are interesting, and the findings derived from them provide us with something interesting to talk about with other

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smokers while we smoke. But the human race has already tried out the tobacco experiment and finds perhaps something like this: smoking does not do a great deal of good but it does not do a great deal of harm. Most members of the same race, smokers included, would also agree that smokers in general would be much more widely tolerated by other members of it if they would bury their butts six feet underground." page 355, (3663)

(3789) Rolleston; London

"At the opening meeting of the session on Oct. 6th, with Dr. J. H. Pendered, the president, in the chair, a paper on the *Tobacco Problem* was read by Dr. J. D. Rolleston (London), who maintained that the subject of tobacco-smoking should be quite as much a concern of public health as the acute exanthemata, diphtheria, the continued fevers, and other forms of infectious disease - a view which appeared to be gaining ground in Germany, where many public health authorities were of opinion that the damage due to nicotine was as great as that caused by alcohol. In this country, however, the tobacco problem like that of alcohol did not seem to have received any recent recognition in public health circles. Apart from the Society for the Study of Inebriety and Drug Addiction, the subject of smoking, of which the late Prof. W. E. Dixon of Cambridge had said that the medical profession could occupy itself with none more important to the nation, like until recently any aspects of the sexual question, had been taboo in medical societies. Dr. Rolleston dealt with the incidence of smoking in different countries and religious denominations, and drew attention to the prevalence of the habit in school-children of the continent, especially in Holland and Soviet Russia. He was inclined to regard smoking as an addiction, if Dr. E. W. Adams's recent definition of addiction be accepted as 'a state of bondage to a masterful drug, manifested by craving, tolerance, intense discomfort of a specialized character on withdrawal of the drug and a tendency to relapse.'" page 908, (3789)

(3790) Rolleston; Western Hospital, London

"Kulbs attributes the recent great increase in smoking in Germany, especially of cigarettes, to the much greater devotion than in the past of the German youth to sport, which diverts them from alcohol, but attracts them to nicotine, in spite of its deleterious effect upon their athletic capacity. In an inquiry made

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fast laws. ... On the respiratory tract, tobacco-smoking is responsible for pharyngeal catarrh which may spread to the larynx and bronchial tubes, causing cough, hoarseness, bronchial catarrh, and so emphysema of the lungs. The irritating effect on the throat and upper air passages exerted by cigarette smoking has been ascribed to furfural, pyridine, and ammonia, and not to nicotine." pages 961, 965, (2632)

(3047) Rolleston; University of Cambridge

"Tobacco and Public Health. While in Britain tobacco like alcohol has received rather a 'step-motherly' treatment in most text books on public health, more attention has been given to the subject in the United States where such well known writers as Milton J. Rosenau and Park devote considerable space to tobacco in their text books, emphasizing the fact that tobacco is in no way an aid to health. Fisk writing in Park's text book, claims that if the sedative effects of tobacco are real and dependable they should be made available in exact dosage and applied therapeutically, whereas if they are not real and dependable in a medical sense they are not real and safe as a mere drug indulgence. In view of the difficulty in determining years in advance whether an individual possesses sufficient resistance to make 'moderate' smoking comparatively harmless, Fisk recommends that the smoker should undergo a thorough physical examination periodically in order to detect any ill effects of tobacco on the circulation. Lickint has recently made enquiries of 100 men over 90: (1) whether they had ever smoked; and (2) whether they still continued the habit with the following results: - This table shows that 22 per cent. of the men over 90 had always been non-smokers, while 36 per cent. had always been smokers. Lickint's investigations during the last few years have shown that the percentage of non-smokers in the male sex has ranged from 5 to 8 per cent. The large number (64) of old men who were not smokers was due to the fact that with increase in age many lost their taste and toleration for tobacco. Most of the old smokers used pipes, a smaller number cigars and pipes and a few only cigars, but none of them smoked cigarettes, which is to be explained by the fact that on the introduction of cigarettes into Germany the men were already too old to change their habits. None of them inhaled. Lickint maintains that as inhaling is generally regarded as the most injurious form of smoking the prognosis of duration of the life of most smokers today is less favorable than before, in view of the

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see marked improvement in those who are wise enough to follow his advice; and, if he is not a tobacco addict himself, he will find what a 'strangle hold' tobacco has on the great majority of its victims, many of whom admit that they would risk being sick, or hazard life itself, rather than give up the use of tobacco. When the above facts are remembered, Professor Raymond Pearl's studies are even more convincing that the use of tobacco, even moderately, decreases longevity and that the excessive use of tobacco shortens life very materially." pages 281-281, (3973)

(3974) Head; Northwestern University Medical School

"As vices go, it is probably comparable to the common cold among illnesses. But the common cold, while not threatening life, is, because of its prevalence, a very important disease, accounting in the aggregate for a tremendous loss of working time and a still greater loss of working efficiency. Smoking similarly, while rarely causing serious consequences, certainly is a bad thing for the individual and for the race. It is not an especially strong habit. While it is uncommon to find anyone who inhales who stops permanently, many do stop for long periods. Those who stop permanently do so usually because they have been frightened by symptoms attributed to smoking. Deprivation causes discomfort but no serious manifestations." page 285, (3974)

(4004) Gottsegen; Columbia University, New York, NY

"However, smokers are not more susceptible to cancer of lips, tongue, mouth, throat, lungs and esophagus. Tobacco acts only occasionally as an irritant and is not necessarily a determining factor. This conclusion is corroborated not only by clinical evidence but also by statistical data. In those parts of the world, where women are heavy smokers, as in Brittany, Holland, Asia and Africa, cancer of the tongue is not more frequent in women than elsewhere. Moreover, despite an increase of smoking, there is no similar increase in mortality from cancer of tongue, lip, mouth and jaw. In 1934, the New York City Health Department also reported a decrease in the number of the above types of cancer for women." page 94, (4004)

(4064) Myers; Kansas City, MO

"Improved methods of diagnosing, instead of inhaling smoke, may explain the constantly increasing

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in the United States by Karp among twenty-four smokers as to why they smoked, thirteen replied that it was merely for the pleasure of it, six put forward its soothing and restful action, and five maintained that it promoted sociability. It is probable, indeed, that many indulge in the habit, not because it gives them any pleasure, but from a reluctance to appear conspicuous, eccentric or self-righteous by their abstinence. The influence of the massive suggestion exercised by the ubiquitous advertisements of different brands of cigarettes must also not be forgotten." page 44, (3790)

(3791) Rolleston; Western Hospital, London

"Respiratory System. - Medical opinion is divided as to the effect of the tobacco habit on the respiratory system. Lambert Lack, for instance, in 1905, and Johnson, in 1929, were inclined to the view that the evil effects of smoking on the throat has been greatly exaggerated, and maintained that the chief effect of tobacco was a local one exerted mainly on the pharynx, less frequently on the larynx, exceptionally on the trachea, and seldom, if ever, on the lungs. On the other hand, Hanau declares that nicotine has not only a superficial caustic action on the mucous membrane of the respiratory tract, but also a deeper action on the bronchial wall, vessels, nerves and smooth muscles when the smoke is inhaled. Chronic bronchitis, bronchospasm and a relaxed condition of the bronchi are also attributed to the inhalation of cigarette smoke by Hildebrandt. As the effect of smoking is irritation of the larynx and bronchi, and its antiseptic action is practically nil, Pouey maintains that the tuberculous patient should be strictly forbidden to indulge in the habit. On the other hand, Duboff found that laryngeal complications in pulmonary tuberculosis were not more frequent in smokers than in non-smokers." page 465, (3701)

(3871) Boland; Guy's Hospital, London

"You will find no difficulty in finding plenty of poems and essays singing the praises of tobacco. On the other hand, you will seek in vain for any books written in defence of it, although books written to condemn it are legion. This disparity is produced as evidence by one of the spokesmen for the anti-tobacconists. He said that this showed that there was no case to be made out for tobacco, and that this proved its badness; but the smoker is, perhaps to his detriment, a philosophical

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induction of lung cancer cannot definitely be ascribed to tar, although it is possible that it is active in combination with other factors. The effect of smoking may be similar now that Schurch and Winterstein, as well as Roffo have induced skin cancer by the use of tobacco tar." pages 37-38 of English translation, (4267)

(4319) Amberson; NIH and Baltimore City Hospital, MD

"The cause of cancer of the lung is no better understood than that of other cancers. Suspected but unproved factors include preexisting chronic inflammatory lesions and the prolonged inhalation of irritating dust. The evidence is somewhat more convincing that the prolonged inhalation of dust of radio-active ores predisposes to cancer. Recently a number of writers have indicted tobacco smoke and the fumes of automobile exhausts." page 329, (4319)

(4336) Harnett; British Empire Cancer Campaign

"Kennaway classified the occupations of 18,280 persons dying from carcinoma of the respiratory tract for the years 1921-32. He found that in all occupations where there is exposure to road dust (pavers, road sweepers, horse and motor drivers) there is a high incidence of carcinoma of the lung. Most dusty occupations show no great frequency, with the exception of metal grinders, who are liable to fibrosis of the lung from silica dust, and in them the frequency of lung carcinoma is 2-1/4 times normal. Available data suggest coal tar, whether from road, chimney, or any other source, does not cause carcinoma of the lung; it is noteworthy that cotton mule spinners have an especially small liability, though they inhale air sprayed with carcinogenic oil. ... In occupations involving much inhalation of dust, there were 4 coal miners, 4 grinders, 3 chimney sweeps and 2 horse transport drivers. Agricultural work was represented by 7 gardeners and 6 farmers or farm labourers, and workers in gasworks by 5. In the absence of control figures of the occupations of all patients attending London hospitals, it is impossible to say whether these figures show any significant deviation from the average. 80 per cent. of the patients were town dwellers and 18 per cent. lived in the country. ... The percentage of smokers was estimated in group of 69 men and 18 women, mostly from one hospital. Of the men 4.3 per cent. were non-smokers, 26.1 per cent. moderate, and 40.5 per cent. excessive smokers (over 3 oz. of tobacco per week), with 29 per cent. not

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person; he seeks no converts, and in the face of all fulminations continues to smoke his pipe in unruffled peace. You will notice, therefore, that all the books which are written about tobacco are, in fact, written against tobacco, and you will look in vain for any dispassionate study unless you can find impartiality in M. Poucel, who starts his books by saying that he will consider the question without bias and without any preconceived prejudice, and then refers to it as 'This scourge ...' on about the third page! All writers appear to be singularly unanimous not to say imitative in their charges against tobacco. I will endeavour to summarize them, as it would take much too long to recapitulate all of them. Starting with the respiratory system first of all, they state that it produces chronic laryngitis, chronic bronchitis and all the complications that come in its train; that it aggravates the disease of the tuberculous and predisposes them to tuberculous laryngitis, and that it may be an important factor in the production of growths of the lung." page 226, (3871)

(3973) Harris; President, Alabama Med. Assn., Birmingham, AL

"When the effects of tobacco on the human body are considered, and also the fact that every smoker, during the twenty or thirty years while he poisons himself slowly with nicotine, contributes at least \$1,000.00 to plutocratic tobacco manufacturers, it is evident that Barnum's estimate of a sucker result of the high powered advertising campaign to teach women and girls to smoke, the use of cigarettes has increased ten fold; and an estimate of 'a sucker born every second' does not overestimate the number of gullible men, women and children who have 'swallowed the bait, hook and line' of tobacco manufacturers. Tobacco would not be used by civilized people if it were not that the manufacturers and advertisers of cigarettes and other forms of tobacco propose to make money, without regard to whether or not the product they manufacture and advertise is harmful to, and shortens the life of, those who form the nicotine habit. The young physician, before he becomes an abject slave to tobacco - and therefore incapable of forming an unbiased opinion on the physiologic and pathologic effects of nicotine - should study recent clinical investigations regarding tobacco as a cause of disease. In making his case histories he should record the number of cigarettes, or the amount of tobacco in any form which the patient uses, and then try to persuade the victim to give up tobacco. Usually he will

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carcinogens were already known prior to 1950 and were reinforced by additional studies from 1950 to 1966. The acceptance of cigarette smoking as a cause of lung cancer in a particular patient continued to be challenged by coincidental exposure of the patient to occupational/environmental factors.

Monographs on Occupational Cancer

In the *History of Cancer Control in the United States, 1946-1971*, Agran reviewed the history of cancer in workers starting with the 1775 discovery of Percival Pott of scrotal cancer among chimney sweeps (7701). Pott's findings coincided with the onset of the industrial revolution and was followed by discoveries of cancers in other groups of workers. Agran described the first comprehensive monograph written in the United States as follows:

"After this four-year research effort - the German-born Hueper later described it as looking for 'one piece of dirt leading to another' - he had amassed the evidence necessary to write a monumental 896-page tome entitled *Occupational Tumors and Allied Diseases*. Published in 1942, the book, like Hoffman's earlier work, documented the existence of a series of high-risk occupations for cancer. But Hueper went further; he identified the suspected or recognized cancer-causing agents (carcinogens) associated with certain occupational cancer epidemics, and he argued for a cancer prevention strategy consisting of effective control measures to match the hazards of what he termed 'the new artificial environment.'

Just as scientists learned in the nineteenth century that numerous pathogenic micro- and macro-organisms were the environmental agents of serious disease, so too, Hueper argued, the steady increase in the incidence of cancer since 1900 was due to the interaction of the human cells with a burgeoning variety of specific chemical and physical agents, some of them highly carcinogenic.

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reviews, how did medical authors relate occupational/environmental factors to cigarette smoking in discussion of pulmonary carcinogenesis? Did the article belong to any of the following: Group (a) Health hazards of occupational/environmental factors reviewed but no mention of cigarette smoking (4 publications); Group (b) Health hazards of occupational/ environmental factors with tobacco smoking mentioned but no opinion on preferential cause (19 publications); Group (c) Questions health hazards of occupational/environmental factors with no mention of tobacco smoking (1 publication); and Group (d) Questions health hazards of occupational/environmental factors with mention of tobacco smoking (2 publications).

Group (a) Articles on health hazards of occupational/
environmental factors with no mention of tobacco smoke.

(4023) Biederman; New York, NY

"The industrial activities are definitely placed as causative factors. In the Schneeberg district, Bergkrankheit has been recognized as an industrial disease which has been shown to be cancer of the lung. A large proportion of the mining workers die of this 'chronic pulmonary disease.' Insufficient protection against dust allows sharp particles to be inhaled and these irritate the bronchial membranes. Kennaway and Kennaway by studying statistics on death certificates found that road workers, metal grinders and employees in gas works were most frequently involved." page 420, (4023)

(4087) Singer; Cedars of Lebanon Hospital, Los Angeles, CA

"Occupation. - The occupation of patients who have carcinoma becomes important, particularly when carcinoma apparently follows some traumatic injury; especially for those persons who work where there is a hazard of trauma, particularly in coal mines, in an atmosphere of

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railway officials, agents and brokers, teachers, bank officials, civil servants, farmers, etc. Although these differences are statistically significant, the occupational factor responsible for them are uncertain; occupations are often difficult to classify with precision, people change their occupations, and as regards tumour causation occupation earlier in life is more important than that engaged in later and recorded on a death certificate. However, the many occupational differences revealed by analyses such as the Registrar-General's afford hints of possible carcinogenic factors which are worth further statistical and experimental investigation. It is important to emphasize here the great length of the latent period often intervening between the application of the carcinogenic stimulus and the eventual appearance of the tumour. This makes it useless to look for the causes of human tumours in the occupations and habits of affected persons during the parts of their lives immediately preceding the appearance of their tumours. The tumour of today is often the consequence of stimuli applied 10, 20 or 40 years ago. Our medical histories, and therefore our statistical data, of tumour patients are often totally deficient in this respect; detailed inquiry into the occupations and habits of the whole of the patient's previous life, remote as well as recent, is rarely undertaken. Here is a great almost virgin field of research, exploration of which by competent workers with a full knowledge of the problems involved must be undertaken if we are to sift out of our complex environment the carcinogenic factors which are yet unrecognized. And the same applies to the elucidation of the causes of many other chronic diseases - blood dyscrasias, hepatic degeneration and cirrhoses, endocrine disorders, and chronic renal and arterial disease." page 87, (4802)

Willis was paraphrasing contents of his own article and those by British epidemiologists such as Heady (4939).

Tabulated Opinions on Occupational/Environmental Factors

The grouping of articles initiated for the 1930's (Chapter III, page 267) is being followed presently for the purpose of answering the following question: Outside of monographs and

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exposed mice to an atmosphere containing much tar and no carcinoma was found. Carcinoma is common in Russia, where almost no tar is used. The importance of automobile gas fumes has been discussed but it is significant that the occurrence of the lesion is no more common among garage mechanics and truck drivers than in the general population. War gases have been mentioned but their importance seems to be slight. The same is true of tobacco smoke. It may be an irritant but it probably is not an important factor. If tobacco were the cause of lung cancer, why has not carcinoma of the lips and tongue increased at a rate parallel with carcinoma of the lung." pages 2781-2782, (4233)

(4267) Wogelin; Pathological Institute, Berne, SWI

"Given the known carcinogenic action of tar, it is understandable that this substance should be given special attention in the case of lung cancer as well. However, it has been observed in animal experiments that lung cancers are often observed in mice whose skin had been painted with tar and in certain mouse strains with special predisposition to lung tumors, the number of lung cancers may increase enormously. In humans, an analogous case was reported by Mullschitzky, concerning a tar worker who contracted cancer of the scrotum 15 years earlier, cancer of the penis two years later and then keratomas on the face and wrists, and cancer of the earlobe, finally dying of the primary bronchial cancer. Transfer of the tar substances in the blood and excretion via the lungs is the most likely explanation for the localization of the cancer if the respiratory tract, since even intravenous injection of carcinogenic hydrocarbons results in lung tumors in mice. However, direct injury from inhaled tar particles is most likely in the case of human lung cancer, and tar spraying of the roads is indicated for this. Probst, however, showed that the increase in lung cancers began in Zurich even before tar spraying was used on streets and roads. In Denmark, Husted and Biilmann also failed to find any correlation with street tar spraying, and the increase in lung cancer is noted even in countries where street tar spraying has been performed only to a limited degree, such as, for example, in Russia. Following the experimental inhalation of road dust, Campbell observed lung cancer in mice, and the percentage was higher for tar-containing dust than for dust purified of tar. Intratracheal and intra-pulmonary injection of dibenzanthracene and other carcinogens yielded positive results in some cases and negative results in others. Accordingly, a role in the

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